REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 20-25 and 27 are pending. Claim 26 was previously cancelled. Claims 20-24, 25, and 27 are currently being amended. Claim 20 has been amended to clarify that a biological sample from the human to whom the labeled ligand was administered is assayed so as to determine the level of ligand binding. Accordingly, the level of labeled ligand is an indicator of the level of VEGF in the biological sample. An over-abundance of VEGF in the biological sample, relative to the level of VEGF in a person not suffering from cancer, is an indicator of an "abnormal presence" of VEGF in the biological sample. This amendment is fully supported by the specification. See, for instance, page 6, lines 9-16 and page 11, lines 25-35.

Claims 21 and 22 have been amended to replace the phrase "overexpression" with "abnormal increase in expression of" to ensure there is correct antecedent basis with respect to claim 20.

Claim 23 has been amended to recite a "labeled ligand" instead of "the presence of the ligand" to ensure there is correct antecedent basis with respect to claim 20.

Claim 24 has been amended solely for grammatical reasons and is fully supported by the specification. See, for example, page 23, line 15 to page 24, line 7.

Claim 25 has been amended solely for grammatical purposes.

Claim 27 clarifies that the labeled ligand is detected in a bodily fluid. See page 11, lines 3-5 for support.

II. Claim 27 is enabled

Examiner Holleran maintained her rejection of claim 27 under 35 U.S.C. 112, first paragraph because Applicant's previous response "fails to address the failing of the specification to teach what constitutes an 'abnormal presence' of the labeled ligand in a bodily fluid." Office Action dated July 2, 2003, at page 2.

According to the Examiner, "[B]ecause the label will be found in all bodily fluids whether there is metastasis of not, it is not clear that the specification apprises one of skill in the art how to detect metastasis by the detection of label in a bodily fluid." Office Action at page 3.

Applicant respectfully disagrees and traverse the rejection. It is clear that one aspect of the present invention is the determination of the level of VEGF in a sample obtained from an individual, wherein an "over-abundance" of VEGF in comparison to a normal, non-cancerous sample, indicates an "abnormal presence" of VEGF in the biological sample. Thus, Applicant states at page 6, lines 9-16 of the specification that "[I]n one aspect of the invention, the level of VEGF expression in a human with a cancerous condition is detected and monitored. Because abnormal increased expression of VEGF by a tumor triggers the onset of angiogenesis, the level of VEGF is a molecular marker for the progression of the cancerous condition" (emphasis added).

Without acquiescing to the Examiner's reasons for rejecting claim 27, Applicant has deleted the qualifier "abnormal presence" and clarified the positive step to reflect that a level of labeled ligand in the biological sample that is greater than the level of the labeled ligand in a non-cancerous biological sample indicates an abnormal increased expression of VEGF relative to the non-cancerous tissue, at a site distal from the primary tumor and further indicates the presence of metastasis in the human.

Since the amendment is fully supported by the specification and merely clarifies the term "abnormal presence," Applicant respectfully requests that the Examiner withdraw this rejection.

III. Claims 20-25 are not rendered obvious over Boocock in view of Ferrara

Examiner Holleran maintained her rejection that claims 20-25 are unpatentable under 35 U.S.C. 103(a) over Boocock, J. Nat. Cancer Inst. 87(7):506-516, 1995, in view of Ferrara, WO 94/10202, published May 11, 1994.

The Examiner was unpersuaded by Applicant's arguments and states that "the teachings of Boocock establish the association between VEGF and the condition of metastasis. Now that this association has been established, using the detection of VEGF as a way of detecting metastasis is obvious, especially in view of teachings establishing that methods of VEGF detection are known in the art." Office Action at page 3.

There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the combined art must teach or suggest all the claim limitations.

However, as Applicant has made clear, neither prior art reference suggests nor motivates *the **detection** of metastasis* as is presently claimed. The present invention claims a method for detecting metastasis by quantifying or qualifying, *i.e.*, visually or colorimetrically, the relative amount of VEGF in a human. If that level of VEGF is above what is considered normal for a non-cancerous human, then that elevated level of VEGF is an indicator of metastasis.

The biological samples assayed by Boocock, however, were already diagnosed as metastatic. "[W]e aimed to clarify the function of VEGF in tumor development by identifying the cells in ovarian carcinoma tissue that expresses VEGF and its receptors" (emphasis added), see the abstract; and almost a year earlier, Ferrara taught that an antibody or hVEGFr labeled with a detectable moiety could be used for *in vivo* imaging. However, neither Boocock nor Ferrara suggest assaying or "imaging" a human in whom a metastatic state has not been previously identified.

At most, the person of ordinary skill, from having read Boocock and Ferrara, would have been prompted to modify Boocock by administering to a patient, diagnosed with having metastatic tissue, Ferrara's antibody or hVEGFr labeled with a detectable moiety so as to image VEGF distribution. There is nothing in either reference to suggest comparing the level of the labeled moiety to levels obtained from a control patient in whom there is no metastasis. Indeed, there would be no need for the skilled artisan to determine if metastasis was present in the patient because Boocock teaches that metastatic tissue is the starting material for their analysis.

The Examiner states that Boocock establishes the association between VEGF and the condition of metastasis. However, the "implications" of Boocock's published research was that "coexpression of VEGF and KDR by tumor cells in ovarian carcinoma raises the possibility of autocrine stimulation and of therapeutic strategies targeting this receptor-ligand interaction." See the last line of the Boocock abstract. There is no suggestion that VEGF levels can be used as an indicator of metastasis as is presently claimed.

Furthermore, the Examiner has used impermissible hindsight in arriving at her conclusion. As she is well aware, a proper determination under 35 U.S.C. 103, requires the examiner to step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination.

Applicant's claimed invention "as a whole" requires administering to a human a detectably labeled ligand which specifically recognizes VEGF; and detecting the labeled ligand in the human, wherein a level of labeled ligand that is greater than the level of the labeled ligand measured from a non-cancerous human is indicative of an abnormal increase in expression of VEGF, which is an indicator of metastasis.

Neither reference teaches, suggests, or motivates such an invention and, therefore, no combination of the references renders the present claims as obvious. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 2/27/04

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